1108-126 The Effect of Physical Exercise on Circulating Chromogranin A Levels in Patients With Congestive Heart Failure

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Background: Chromogranin A (CgA) is widely distributed throughout the neurendocrine system and may, due to its long in vivo and in vitro half-life, be an attractive candidate for assessment of neuroendocrine activity in congestive heart failure (CHF). Recently, increased plasma levels of CgA have been found in patients with CHF and related to the severity of symptoms and prognosis. The effect of physical exercise on circulating CgA levels in patients with CHF is unknown. Moreover, the relation between CgA levels and invasive hemodynamic indices remains to be established.
Methods: 22 patients with chronic CHF (NYHA class II- IV) performed supine bicycle testing with breath-to-breath analysis for assessment of peak oxygen uptake (VO_2 max). Venous blood samples for CgA analysis were drawn at baseline, at peak exercise, and 1 hour post-exercise. Plasma levels of CgA were determined by radioimmunoassay. Echocardiography and left-and right cardiac catheterization were performed in all patients. 10 healthy age- and sex matched volunteers served as controls.
Results: CHF patients had reduced peak VO_2 compared to controls (13.6 ± 5.4 vs 31.5 ± 10.0 ml/kg/min, p<0.001). The baseline level of CgA was elevated in patients compared to controls (24.3 ± 14.4 vs. 18.7 ± 1.5 ng/ml, p< 0.05). Baseline levels of CgA correlated positively with arteriovenous O_2 difference (r = 0.62, p = 0.02) and negatively with LVEF (r = -0.70, p< 0.001). CgA did not correlate significantly with pulmonary capillary wedge pressure, right atrial pressure, stroke volume, cardiac index or peak VO_2. Whereas CgA levels increased significantly from baseline to peak exercise in control subjects (from 18.7 ± 1.5 to 22.0 ± 3.6 ng/ml, p< 0.05), the CgA response to exercise was blunted in CHF patients (from 24.3 ± 14.4 to 24.4 ± 15.6 ng/ml, p = ns).
Conclusion: CgA levels are elevated in patients with CHF and are related to left ventricular systolic function and arteriovenous O_2-difference. The CgA response to exercise is blunted in CHF, suggesting widespread baseline neuroendocrine activation in CHF. In contrast to catecholamines, circulating CgA concentrations are not affected by physical activity in patients with CHF.

1108-127 Determinants of Exercise Capacity in Hypertrophic Cardiomyopathy Are Different in Patients With or Without Heart Failure

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Background: Mechanisms of exercise intolerance have been previously studied in hypertrophic cardiomyopathy (HC), but have yielded conflicting results. Aim of this study was to ascertain whether determinants of exercise capacity differ in HC pts with or without symptoms and signs of heart failure.
Methods: We studied 25 HC pts (15 males, age: 43±7 yrs, Gr.A) with functional class I and normal LV function (i.e. baseline LV ejection fraction>50%), as well as 10 HC pts (6 males, age: 45±8 yrs, Gr.B) with functional classes II or III and LV dysfunction (i.e. baseline LV ejection fraction<50%). All pts underwent symptom-limited supine bicycle exercise (25 watt every 2 minutes) with post-exercise Doppler echocardiography. Exercise duration ranged from 180 to 610 s (mean: 480±223 s).
Results: Both in Gr.A and in Gr.B, no relation was found between exercise time and measurements of cardiac morphology (i.e. maximal LV wall thickness: r=0.05 and r=0.09, respectively; LV wall thickness index: r=-0.11 and r=0.03; RV end-diastolic diameter: r= -0.17 and r=0.13; LV end-diastolic diameter: r= 0.21 and r=0.29), cardiac function at rest (i.e. RV ejection fraction: r=0.22 and r=0.15; LV ejection fraction: r=0.27 and r=0.23), and Doppler indexes of LV diastolic filling (i.e. peak E-wave: r=-0.21 and r=0.25; peak E-wave: r=-0.09 and r=-0.15; E/A ratio: r=0.16 and r=0.25). Multivariate analysis showed that the only independent predictors of exercise capacity were: (i) in Gr.A, the extent of changes recorded at peak exercise in LV ejection fraction (p=0.01) and LV end-diastolic volume (p=0.02); (ii) in Gr.B, the extent of changes recorded at peak exercise in RV ejection fraction (p=0.01).
Conclusion: Determinants of exercise capacity in HC are different in pts with or without symptoms and signs of heart failure. In asymptomatic pts with normal LV function, exercise tolerance relates to the ability of the LV to increase its volume with exercise in order to augment LV ejection fraction. In pts with mild-to-moderate heart failure and LV systolic dysfunction, conversely, exercise capacity depends on a preserved RV function, which can maintain an adequate pre-load on exercise.

1108-128 Myocardial Stunning in Hypertrophic Cardiomyopathy Is Associated With Progression to Mild-to-Moderate Heart Failure

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Background: Myocardial stunning can occur in multiple cardiac diseases and has been previously observed even in pts with hypertrophic cardiomyopathy (HC). Recently, the phenomenon has been related to progressive deterioration in LV function in ischemic heart disease. Aim of this study was to test the hypothesis that the progression to heart failure in HC pts is associated with myocardial stunning.
Methods: We studied a total of 30 pts with nonobstructive HC (mean age: 45±12 years), no heart failure, normal coronary angiograms, and normal LV function at baseline but with no exercise-induced increase in LV ejection fraction. All pts underwent, off-drugs, two consecutive symptom-limited bicycle exercise tests (i.e. workload increase of 25 watts every 2 min), one-hour apart. Doppler echocardiography was performed at baseline, at peak exercise, and every 30 min after each test, and LV ejection fraction and Doppler measurements of LV diastolic filling were derived. Myocardial stunning was diagnosed if a more prolonged deterioration in LV systolic and diastolic function was detected after repetitive exercise than after the initial exercise test.
Results: At baseline, myocardial stunning was seen in 10 pts (Gr.A) but not in the remaining 20 pts (Gr.B). Compared with Gr.B, Gr.A pts were significantly older (56±14 vs 45±15 years, p<0.05), had higher maximal LV wall thickness (22±5 vs 17±6 mm, p<0.05), and lower LV ejection fraction (58±8 vs 68±10%, p<0.05). Over a 5-year follow-up period, symptoms of mild-to-moderate heart failure developed in 7/10 Gr.A pts (70%) and in 4/20 Gr.B pts (20%). Progressive LV function deterioration (i.e. decrease of ejection fraction10%) occurred in 3 and 2 Gr.A pts, respectively, but were not observed in Gr.B.
Conclusion: Our results confirm that significant myocardial stunning can occur in a subset of pts with HC and is associated with worse functional status and outcome. Repetitive episodes of myocardial ischemia during daily life may play a previously unrecognized pathophysiologic role in determining the progression to mild-to-moderate heart failure in HC.

1108-129 Left Atrial Enlargement in Hypertrophic Cardiomyopathy: The Importance of Left Ventricular Hypertrophy and Diastolic Dysfunction

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Background: Left atrial (LA) enlargement (LAE) in patients (Pts) with hypertrophic cardiomyopathy (HCM) is associated with increased morbidity and mortality. We analyzed factors related to LAE.
Methods: 84 pts with HCM were divided into two groups based on the anteroposterior LA diameter measured by 2D echo: Group A (n=30) with LA ≤ 40mm and Group B (n=54) with LA >40mm. Left ventricular (LV) wall thickness (LVWT, mm) was measured at 15 sites of LV wall segments: 5 walls (anterior and posterior septal, anterior, lateral, posterior) at 3 levels (base, mid and apex). Mitral peak filling velocity and tissue Doppler (TDI) peak velocity at lateral annulus (E', both cm/s), basal septal (IVS, mm), average LVWT of 15 sites (Avg-LVWT, mm), and LV outflow tract rest pressure gradient (LVOT-PG, mmHg) were measured. Wigle hypertrophy point score (0-10), E/E' and TDI derived LA pressure(mmHg) were calculated.
Results: Both groups had a similar degree LVOT-PG (14±17 vs 21±24, p<0.05) and syncope (30% vs. 27%, p>0.05). Patients with larger LA had a worse functional class (NYHA), a higher prevalence of atrial fibrillation (AF) and more LV hypertrophy with greater LVWT in all non-apical wall segments (p<0.05 to p<0.0005). LAP, IVS, Avg-LVWT, Wigle score and E/E' differed between the two groups.

Table: *p<0.05, **p<0.001 compared between the two groups

	NYHA	AF(%)	Scores	IVS	Avg-LVWT	LAP	E'	E/E'
LA≤40	1.4±0.6	0	3.9±2.1	16.3±3.4	11.7±1.7	11.6±3.1	9.6±2.8	7.6±2.4
LA>40	1.8±0.8 **	17*	6.2±2.1**	20.5±5.0**	14.0±2.5**	14.8±7.0**	8.0±2.8**	10.2±5.6**

Conclusions: In pts with HCM, LAE is associated with worsened clinical status and quantitative echo demonstrated more severe LV hypertrophy in all non-apical segments and more severe diastolic dysfunction with elevated filling pressures.

1108-130 Granulocyte-Colony Stimulating Factor Mobilizes Bone Marrow Stem Cells and Favorably Alters Cytokine Profile in Patients With Advanced Heart Failure

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Background: Recent reports indicate that stem cell mobilization with granulocyte-colony stimulating factor (G-CSF) leads to repair of the infarcted myocardium in animal models. We conducted a phase I/II study of G-CSF in advanced heart failure patients to determine if bone marrow stem cells could be safely mobilized in this group of patients.
Methods: Patients with advanced heart failure (n=6; mean age 63±4.2 years; range 54-82 years; New York Heart Association Class IIIB) with previously implanted defibrillators were admitted to the General Clinical Research Center for the duration of G-CSF administration (5 µg/kg/day for 5 days),and serial measurents of stem cell and cytokine response were done, in additon to safety parameters.
Results: Peripheral stem cell count increased in all patients above the predetermined efficacy parameter of 10 cells/µl. The mean stem cell count increased from 3.6±0.5/µl to 37±13/µl (p=0.022), with a parallel increase in WBC count from 7±1 x 10^3/ mm^3 to 42±8 x 10^3/mm^3 (p=0.002). There was no significant change noted in the plasma levels of IFN-γ, TNF-α, IL-2 and IL-4. Interestingly, plasma IL-10 level increased from a baseline mean value of 4.24+/- 0.38 pg/ml to a mean peak value of 9.36 +/- 1.13 pg/ml (p=0.003) by 10 days after initiation of study drug administration, and came down to baseline by 6 weeks.There was an asymptomatic reversible elevation of alkaline phosphatase in all patients. In one patient, worsening heart failure and renal dysfunction developed, which was rapidly reversible.
Conclusions: In spite of severe heart failure, there was significant mobilization of stem cells into the peripheral circulation with a low dose of G-CSF. In addition, G-CSF favorably altered serum cytokine profile in advanced chronic heart failure, with an increase in the anti-inflammatory cytokine IL-10, and unaltered levels of pro-inflammatory cytokines